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Cognitive Behavioral Therapy for antipsychotic-free schizophrenia spectrum disorders: Does
therapy dose influence outcome?

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Dear Editor,

The benefits of Cognitive Behavioural Therapy (CBT) for schizophrenia spectrum disorders have been demonstrated in an open trial for people that chose not to take antipsychotic medication (Morrison et al., 2012) and in a single-blind randomised controlled trial (RCT) known as ACTION (Assessment of Cognitive Therapy Instead of Neuroleptics) (Morrison et al., 2014). The primary outcome measure for the ACTION trial was the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) with an estimated Cohen's d effect size of 0.46 (common to all follow-up time periods), thus demonstrating the value of CBT for psychosis (CBTp) as a stand-alone intervention.

The Lancet Psychiatry Commission for psychological treatments recently stated that “beyond knowing that an intervention is efficacious, research initiatives are needed that clarify the key mechanisms through which interventions work” (Holmes et al. 2018, p.237). Given the majority of RCT's for schizophrenia involve participants taking antipsychotic medication we performed a secondary analysis of the ACTION trial which provided an opportunity to investigate mechanisms of change in the absence of an interaction with such medication.

This study had two aims. The first was to estimate the treatment effects of each additional session of therapy on the PANSS total score. The second was to examine the impact of a range of CBT components (i.e. use of formulation, homework, cognitive techniques) on the PANSS total.

Eligible participants aged 16-65 years had either discontinued antipsychotic medication for at least 6 months whilst experiencing continuing symptoms, or had never taken antipsychotic medication. At entry to the trial all participants scored at least 4 on PANSS delusions or hallucinations, or at least 5 on suspiciousness or persecution, conceptual

disorganisation, or grandiosity. Participants were randomised to either CBT plus treatment as usual (TAU) (N=37) or TAU (N=37).

Participants randomised to therapy received up to 26 sessions of CBT over a period of 9 months, plus up to 4 booster sessions. Treatment components were recorded by the therapists after each therapy session (based on whether the component had been a main focus of the session) and these included formulation (maintenance and longitudinal), homework, agreed goals, cognitive techniques, behavioural strategies and metacognitive strategies. Therapists utilised these components as and when appropriate to the particular problems that emerged. The PANSS was administered at baseline, 3,6,9,12,15 and 18 months. The end of therapy assessment was at 9 months.

Instrumental variable methods were used to estimate the treatment effects of each additional session of therapy attended (Emsley et al., 2010) using STATA's `ivregress` command. The analysis used a two stage least squares (2sls) estimation procedure in which the first stage fitted a linear model for number of sessions on treatment assignment and baseline PANSS score, and saved the predicted number of sessions attended for each individual. The second stage regressed the PANSS score at 18 months on the predicted number of sessions from the first stage and baseline PANSS score.

Second, a latent class subgroup analysis (Dunn et al., 2015) and principal stratification (Frangakis and Rubin, 2002) was used to investigate the effect of each treatment component (such as case formulation, cognitive techniques or behavioural strategies etc.) on outcome.

We found a “dose-response” such that each CBT session attended, reduced the PANSS total score by approximately 0.6 points (95% CI -1.20 to -0.06, $p=0.031$), however no individual treatment components were associated with outcome. It was noted that those who received a longitudinal formulation in the first 4 sessions of CBT had poorer treatment effects

than those who did not, however this finding was not statistically significant (95% CI - 37.244, 6.677, $p=0.173$).

Results suggested that length of therapy predicted a better treatment response which is an important finding, given recent trends in the literature that promote the use of brief CBTp (Hazell et al., 2016; Naeem et al., 2016). However, a key limitation of our analysis is the assumption of a linear effect of number of sessions on outcome, as it is plausible that each session did not reduce the PANSS by an equal amount, but rather that earlier or later sessions accounted for more of the treatment effects, or that people experienced sudden gains (Abel et al., 2016). Our secondary analysis was also limited in terms of the small sample size which meant that problems arose concerning the power to detect treatment effects. It is notable that we did not find expected relationships between formulation and outcome for instance, given that formulation is perceived to be a fundamental process in CBT. On balance, this exploratory look at the data must only be interpreted as suggesting potential hypotheses to be tested in a larger trial for example, that randomises participants to receive differing amounts of therapy. Future larger scale studies are also needed to understand mechanisms of change in CBT to help improve outcomes for people with psychosis.

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